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Cell autonomous and systemic factors in progeria development

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Abstract

Progeroid laminopathies are accelerated aging syndromes caused by defects in nuclear envelope proteins. Accordingly, mutations in the *LMNA* gene and functionally related genes have been described to cause HGPS (Hutchinson–Gilford progeria syndrome), MAD (mandibuloacral dysplasia) or RD (restrictive dermopathy). Functional studies with animal and cellular models of these syndromes have facilitated the identification of the molecular alterations and regulatory pathways involved in progeria development. We have recently described a novel regulatory pathway involving *miR-29* and p53 tumour suppressor which has provided valuable information on the molecular components orchestrating the response to nuclear damage stress. Furthermore, by using progeroid mice deficient in ZMPSTE24 (zinc metalloprotease STE24 homologue) involved in lamin A maturation, we have demonstrated that, besides these abnormal cellular responses to stress, dysregulation of the somatotropic axis is responsible for some of the alterations associated with progeria. Consistent with these observations, pharmacological restoration of the somatotroph axis in these mice delays the onset of their progeroid features, significantly extending their lifespan and supporting the importance of systemic alterations in progeria progression. Finally, we have very recently identified a novel progeroid syndrome with distinctive features from HGPS and MAD, which we have designated NGPS (Néstor–Guillermo progeria syndrome) (OMIM #614008). This disorder is caused by a mutation in *BANF1*, a gene encoding a protein with essential functions in the assembly of the nuclear envelope, further illustrating the importance of the nuclear lamina integrity for human health and providing additional support to the study of progeroid syndromes as a valuable source of information on human aging.

Introduction

The nuclear envelope is a complex structure that surrounds and protects the genome, playing essential roles in its regulation, organization and maintenance [1]. The nuclear envelope is composed of two membrane bilayers with nuclear pores that control traffic in and out the nucleus [2,3]. The nuclear face of the inner membrane is covered by the nuclear lamina, a protein network that provides scaffold for nuclear envelope proteins and chromatin [4]. In humans, three genes named *LMNA*, *LMNB1* and *LMNB2* encode nuclear lamins. Whereas the two B-type lamins are encoded by two independent genes, *LMNB1* and *LMNB2*, the *LMNA* gene encodes lamin A and lamin C proteins by alternative splicing. Mutations in A-type lamins, lamin B and several lamin-binding proteins (emerin, MAN1 and lamin B receptor) have been found mutated in different human diseases which are collectively known as laminopathies [5]. The range, diversity and tissue-specificity of laminopathy phenotypes are providing valuable clues about the cellular functions of lamins and lamin-related proteins.

Key words: alternative splicing, laminopathy, microRNA (miRNA), progeria, senescence, tumour suppressor.

Abbreviations used: BAF, barrier to autointegration factor 1; FACE1, farnesylated proteins-converting enzyme 1; GH, growth hormone; HGPS, Hutchinson–Gilford progeria syndrome; IGF-1, insulin-like growth factor 1; miRNA, microRNA; NGPS, Néstor–Guillermo progeria syndrome; rIGF-1, recombinant IGF-1; ZMPSTE24, zinc metalloprotease STE24 homologue.

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Progeroid laminopathies are human syndromes of accelerated aging caused by defects in the nuclear lamina [6,7]. Among them, HGPS (Hutchinson–Gilford progeria syndrome) is the best known. Affected patients show growth impairment, lipodystrophy, dermal and bone abnormalities and cardiovascular alterations, leading to a shortened lifespan [8–10]. HGPS is caused in most cases by a *de novo* point mutation within exon 11 of the *LMNA* gene encoding lamin A (c.1824C>T; p.G608G) [11,12]. Lamin A undergoes a complex maturation process, including the addition of a farnesyl group and a proteolytic processing event carried out by the metalloprotease ZMPSTE24 (zinc metalloprotease STE24 homologue)/FACE1 (farnesylated proteins-converting enzyme 1) [13]. The G608G mutation activates a cryptic splicing donor site, leading to the accumulation of a truncated form of prelamin A, called LAΔ50 or progerin, which lacks a 50-residue-long fragment containing the target sequence for the final proteolytic step carried out by ZMPSTE24/FACE1. Consequently, this aberrant lamin A isoform remains constitutively farnesylated [14,15].

The use of cellular and murine models of progeroid laminopathies [14–19] has provided valuable information about the molecular alterations involved in progeria, such as the involvement of the p53 tumour suppressor [20], the altered biology of adult stem cells [21] or the presence of metabolic alterations [22,23]. These studies have allowed the

development of the first therapeutic approaches for patients with HGPS [24–28]. Currently, two clinical trials are being carried out based on a combination of statins and amino bisphosphonates, alone or complemented with a low dose of a farnesyltransferase inhibitor (http://clinicaltrials.gov; NCT00731016 and NCT00916747).

Although murine models of progeroid laminopathies have been essential for understanding the pathways and alterations that drive progeria development, important questions remain to be answered, especially those related to the regulatory mechanisms that control and integrate the altered pathways, the specific contribution of cellular and systemic alterations to the progeroid phenotype, as well as the specific function of each nuclear lamina component. In this regard, three recent reports from our laboratory have shed light on these points, highlighting the importance of nuclear envelope for human health [28–30].

An *miR-29*/p53 regulatory circuit involved in aging and chronic DNA damage response

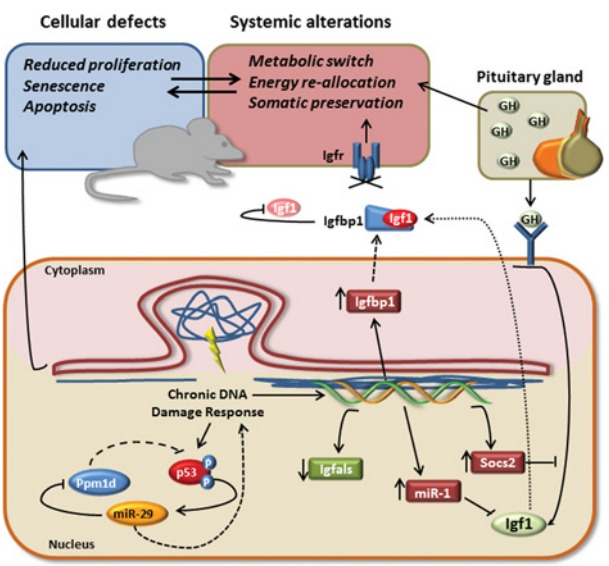
A common feature of aging is the progressive accumulation of cellular damage. Several stressors have been proposed to contribute to this situation, such as oxidative reactions, telomere attrition or the decline of DNA repair and protein turnover systems [31,32]. Progeroid syndromes associated with lamin A alterations show genomic instability as a consequence of the nuclear envelope disruption [33]. This stress triggers a series of cellular and systemic events directed to the restoration of cellular and organismal homoeostasis, which are ultimately responsible for many of the alterations characteristic of these syndromes. In this regard, important changes in chromatin organization and transcriptional profiles have been described in murine models of HGPS [20,34], but little is known about the molecular components that orchestrate these changes.

Over the last decade, miRNAs (microRNAs) have emerged as a new and fundamental level of gene regulation. Each miRNA has the potential ability to repress the translation of hundreds of transcripts and their impact on a great number of cellular processes has been broadly proved. To explore the possible involvement of miRNAs in progeria development, we have performed a miRNA transcriptome analysis in the liver of *Zmpste24*-deficient mice [29]. Among the differentially expressed miRNAs, three of them (*miR-29a*, *miR-29b* and *miR-29c*), belonging to the *miR-29* family, are significantly up-regulated in tissues of *Zmpste24* progeroid-knockout mice.

Through a series of functional analysis, we have found that *miR-29* plays a pivotal role in the regulation of cell survival and proliferation through the modulation of the DNA damage response in a p53-dependent way. Thus the p53-mediated activation of the DNA damage response in *Zmpste24*-deficient cells [35] would trigger multiple effector pathways, including an increase in *miR-29* expression (Figure 1). Among the potential targets of *miR-29*, Ppm1d/Wip1 phosphatase has been proposed as the key mediator for this effect. Ppm1d is a phosphatase that acts as a negative regulator of DNA damage response by dephosphorylating important components of this process such as p53, Chk1 (checkpoint kinase 1), Chk2 (checkpoint kinase 2), p38, γ-H2AX (phosphorylated histone H2AX) or ATM (ataxia telangiectasia mutated) [36,37]. Thus a decrease in Ppm1d levels mediated by *miR-29* would contribute to the activation of the DNA damage response. In agreement with these results, *miR-29* has been described as a tumour-suppressor miRNA in several human cancers. This tumour-suppressive function could be consistent with a pro-aging role for this miRNA, since a growing number of tumour-suppressor genes have been reported to be aging promoters, which could be illustrative examples of the antagonistic pleiotropy phenomenon [38].

Figure 1. | Cellular and systemic alterations involved in progeroid laminopathies

The accumulation of farnesylated forms of prelamin A at the nuclear envelope causes severe alterations in nuclear dynamics, triggering an adaptive response aimed at preserving organism viability under compromising circumstances. At a cellular level, the p53 signalling pathway orchestrates a chronic DNA damage response that involves *miR-29* transcriptional activation. Thus *miR-29*-mediated repression of *Ppm1d* phosphatase reinforces this stress response, favouring a decrease in cellular proliferation rates accompanied by an increase in apoptosis and senescence. These processes result in the loss of tissue and organism homoeostasis. In parallel, a chronic stress response cause changes in the transcriptional profiles of several somatotroph axis key regulators, such as *Igfbp1* (IGF-binding protein 1), *Socs2* (suppressor of cytokine signalling 2), *miR-1* or *Igfals* (IGF-binding protein, acid-labile subunit). These alterations dramatically reduce the levels of circulating IGF-1, which, together with the increased production of GH at the pituitary gland, favours a systemic metabolic switch towards somatic maintenance at the expense of somatic growth.



Somatotroph suppression in *Zmpste24*-deficient mice

Although the dynamics of aging are far from being completely understood, our knowledge of the systemic factors involved in this process has considerably increased in recent years [39–41]. Somatotroph signalling has been identified as a major regulator of longevity from nematodes to humans [42]. Paradoxically, studies in different organisms have shown that the reduction of this signalling is a common feature of both long-lived model organisms and different progeroid mice [43,44].

In this sense, *Zmpste24*-deficient mice show a profound dysregulation of GH (growth hormone)/IGF-1 (insulin-like growth factor 1) balance, with a progressive reduction of blood IGF-1 levels, accompanied by a progressive increase in GH levels and a marked transcriptional alterations in key genes for somatotroph signalling [28] (Figure 1). Thus somatotroph alterations would be responsible for important features of progeroid phenotype such as reduced growth rate and body size. In this case, the observed alterations in somatotropic axis seem to constitute a detrimental phenomenon, rather than a successful adaptive strategy, as demonstrated by the fact that the treatment of *Zmpste24*-deficient mice with rIGF-1 (recombinant IGF-1) is able to ameliorate some of the progeroid features of these mice. rIGF-1-treated mice showed improved body weight, increased amounts of subcutaneous fat deposits, reduced degree of lordokyphosis and alopecia, and significantly extended longevity. Accordingly, rIGF-1 treatment could be a therapeutic approach to slow down disease progression in children with progeria [45].

Interestingly, many pathological features of GH resistance, also known as Laron syndrome, are characteristic of progeroid mice. Both *Zmpste24*$^{-/-}$ mice and patients with this syndrome show reduced muscle development, strength and endurance, as well as decreased bone mineral density, alopecia, skin atrophy and hypoglycaemia [14,22,46]. Some of these alterations could be consequence of an adaptive stress response aimed at preserving organism viability under compromising circumstances by reallocating resources from growth to somatic preservation. In *Zmpste24*-knockout mice, this systemic response could represent an attempt to reduce replication defects, chromosomal instability, nuclear envelope abnormalities and, finally, the risk of developing cancer by decreasing metabolic activity. This hypothesis is supported by the fact that patients with Laron syndrome or other somatotroph-related pathologies such as GH receptor deficiency exhibit a notable reduction in the incidence of malignancies [47,48].

NGPS, a new hereditary progeroid syndrome caused by *BANF1* mutation

The recent availability of high-throughput sequencing technologies has made it possible to address personal genome projects that could uncover the precise causes of human genetic diseases [49,50]. Thus exome sequencing of two unrelated patients that exhibit a progeroid syndrome without mutations in *LMNA* or *ZMPSTE24* has allowed the identification of a homozygous mutation in *BANF1* (c.34G>C; p.A12T), encoding BAF (barrier to autointegration factor 1), as the molecular abnormality responsible for this syndrome [30].

Affected patients of this disease, called NGPS (Néstor–Guillermo progeria syndrome) (OMIM #614008), partially phenocopy HGPS and MAD (mandibuloacral dysplasia), but also exhibit distinctive features, including the absence of cardiovascular alterations and metabolic anomalies, a very severe osteolysis and a relatively long lifespan of affected individuals [51]. NGPS can be considered as a chronic progeria because of its early onset but slow clinical course, which leads to a relatively long survival of patients.

BAF is a small protein (89 amino acids) highly conserved among metazoans [52,53]. BAF binds directly to double-stranded DNA, chromatin, nuclear lamina proteins (including lamin A and emerin), histones and transcription factors, these being required for higher-order organization of chromatin, nuclear envelope assembly, retrovirus infectivity and transcription of specific genes [54].

The A12T mutation in NGPS patients affects a highly conserved residue located at the surface of the protein, decreasing its stability. Skin fibroblasts from these patients show very low protein levels of BAF compared with control fibroblasts and exhibit profound nuclear abnormalities, including blebs and other aberrations associated with progeroid laminopathies. In fact, BAF reduction is correlated with mislocalization of emerin, which shows a predominant cytoplasmic localization in mutant cells. Taken together, these findings demonstrate the relevance of BAF in nuclear envelope dynamics, providing new insights about the relationship of nuclear envelope to aging.

Conclusions and perspectives

Over the last few years, the generation of experimental murine models of progeroid laminopathies has been crucial for a deeper understanding of the molecular basis of these diseases. This is the case for HGPS, where a fast progress has been made in the last 8 years since the identification of *LMNA* mutations to the first clinical trial in HGPS patients. However, new murine models that fully recapitulate all the disease phenotypes of HGPS [55] are necessary to boost the development of *in vivo* approaches directed to the correction of *LMNA* aberrant splicing [25]. Besides, several questions remain to be answered concerning important aspects such as the relative contribution to the progeroid phenotype of cell-autonomous compared with systemic alterations or the involvement of nuclear envelope dynamics during normal aging [56–58].

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